International Journal of Cardiology Sciences

ISSN Print: 2664-9020
ISSN Online: 2664-9039
Impact Factor: RJIF 5.42
IJCS 2024; 6(1): 21-27
www.cardiologyjournals.net
Received: 19-11-2023
Accepted: 25-12-2023

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Role of brain natriuretic peptide as an indicator for reverse remodeling of left ventricular systolic dysfunction after introduction of sacubitril / valsartan in patients with heart failure with reduced ejection fraction

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DOI: https://doi.org/10.33545/26649020.2024.v6.i1a.45

Abstract
Background: Chronic heart failure (CHF) is a clinical syndrome that occurs because of mechanical dysfunction, molecular and inflammatory changes of the left ventricle.
Aims: This study aimed to investigate the effect of Sacubitril/Valsartan on remodelling and serum brain natriuretic peptide (BNP).
Methods: 50 patients with heart failure with reduced ejection fraction (HfrEF) were planned for starting Sacubitril/Valsartan. Echocardiographic parameters for remodelling and Pro BNP level were assessed at baseline and after 6 months.
Results: End diastolic volume (EDV), end systolic volume (ESV) and left ventricular ejection fraction (LVEF) of the patients at baseline were found to be 193.996±69.5142, 142.538±63.7695 and 27.098±7.1668 respectively. After six months, they were found to be 170.546±79.4744, 107.010 ±70.1144 and 40.546±12.8909. Pro BNP at baseline was found to be 1524.78±1922.704. While after six months, it was found to be 594.898±1201.7862 with P value 0.001. Linear regression analysis was done between six months Pro BNP and the factors that showed significant correlations with it. They were 6m New York heart association (NYHA) class, 6m ejection fraction (EF), 6m EDV, 6m ESV, 6m end diastolic dimension (EDD), and 6m end systolic dimension (ESD). Only 6 months EDV, EF and NYHA class are still significantly correlated with the 6 months Pro BNP, so that they can be used as indirect markers for Left Ventricular (LV) remodelling.
Conclusion: The use of Sacubitril/Valsartan in patients with HFrEF resulted in a significant decrease in Pro BNP levels and the reversal of LV remodelling.

Keywords: Natriuretic peptide, heart failure with reduced ejection fraction, sacubitril / valsartan, heart failure, ejection fraction

Introduction

Heart failure (HF) is an escalating global public health issue. Pharmacological treatment for HFrEF has significantly improved during the last four decades. This improvement is linked to decreasing HF clinical outcomes, namely cardiac death and HF hospitalization, together with favorable effects on myocardial remodeling [1].

HF was categorized into three groups: heart failure with decreased ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), and heart failure with moderately reduced ejection fraction (HFmrEF). Some patients with HFrEF may show complete recovery of LV function e.g., those due to viral myocarditis, alcohol-induced cardiomyopathy (CMP) [2].

Plasma concentrations of natriuretic peptides (NPs) are recommended for diagnosis of heart failure, mainly to rule out HF if the results are negative. Elevated concentrations of NPs are essentially useful for prognostication of heart failure as well [3].

There is a correlation between a decline in natriuretic peptide levels over time in patients with HFrEF and better clinical results. However, it remains uncertain whether these alterations in NPs indicate any changes in the structure and function of the heart [4].

The aim of this work was to study pro BNP as an early indicator for reverse remodeling of left ventricular systolic dysfunction in patients with HfrEF after introduction of Sacubitril/Valsartan.

Methods

50 patients presented with HFrEF were planned to start Sacubitril/Valsartan at Cardiology Department, Tanta University Hospitals, during the period of one year starting from June 2021 to June 2022. This study included all HFrEF patients presented with left ventricular EF <35%, stage C heart failure; those with current or prior symptoms of heart failure and NYHA functional class I to IV. Patients were included from both inpatients and outpatients population. Patients with advanced kidney and liver disease were excluded, along with patients with active malignancy, recent coronary revascularization, within one month or if planned for revascularization, patients with valvular or congenital heart disease. Patients were subjected to clinical examinations adressing HF signs and symptoms, staging of HF, NYHA class, neck veins congestion, shifting of the cardiac apex and presence of S3 gallop. ECG and basic laboratory workup including complete blood count, renal profile, electrolytes, liver profile, HbA1c, and coagulation profile were done. Pro BNP testing was done upon recruitment and at 6 months of follow-up. Echocardiography was performed to determine LV remodeling parameters. The following parameters were assessed at baseline and at the 6-month follow-up: left ventricular end diastolic dimension (LVEDD), left ventricular end systolic dimension (LVESD), left ventricular end diastolic volume (LVEDV), left ventricular end systolic volume (LVESV), left ventricular mass (LVM), left ventricular mass index (LVMI), ejection fraction (EF), and left atrial diameter (LAD). Patients receiving angiotensin receptor blockers (ARBs) were shifted to Sacubitril/Valsartan therapy directly. For the switch from angiotensin converting enzyme inhibitors (ACEi) to Sacubitril/Valsartan, a 36-hour wash-out period was mandatory.

Statistical methods

The data were analyzed using the Statistical Package of Social Sciences (SPSS) software, specifically version 20 (SPSS Inc., Chicago, IL, USA). The descriptive statistics for quantitative variables were reported as the mean plus or minus the standard deviation. For qualitative factors, the data were presented as percentages. The student t-test was used to compare the means across groups. The chi-square test was used to analyze the relationship between qualitative variables. The Pearson correlation coefficient was used to examine the extent of linear connection between continuous data. Statistical significance tests were used, and a P value of < (0.05) was deemed to be statistically significant.

Results

The most notable outcome of this study is the significant decrease in Pro BNP levels after the administration of Sacubitril/Valsartan. This decrease was linked to enhancement in the clinical condition and echocardiographic factors that indicate remodeling. Demographic data of the patients are shown in (Table 1), the mean and SD of the age of the patients was 54.18±2.429 years.

Table 1: Demographic data of the study patients

	N	Range	Minimum	Maximum	Mean	Std. Deviation
Age (Year)	50	52	23	75	54.18	12.429
Weight (Kg)	50	95.0	47.0	142.0	81.908	21.2382
Height (M)	50	.3600	1.4800	1.8400	1.644814	.0849561
BSA	50	1.55	1.43	2.98	1.9048	.29996
BMI	50	29.6	19.6	49.2	30.044	5.9367

Data are presented as mean ± SD or frequency (%). BSA: Body surface area, BMI: Body mass index

14 patients (28%) were female. 34% of the patients were hypertensive and 40% were diabetic. 28% of them were having dyslipidemia and the same percentage for history of CAD. 18% of the patients were smokers. (Table 2).

Table 2: Risk factors for CAD and gender

		Frequency	Percent
Obesity	No	29	58
	Yes	21	42
Sex	Female	14	28
	Male	36	72
Hypertension	No	33	66
	Yes	17	34
Diabetes mellitus	No	30	60
	Yes	20	40
Dyslipidemia	No	36	72
	Yes	14	28
Smoking	No	41	82
	Yes	9	18
History of CAD	No	36	72
	Yes	14	28
Prior CABG	No	49	98
	Yes	1	2
Prior PCI	No	43	86
	Yes	7	14

Data are presented as frequency (%). CAD: coronary artery disease, CABG: coronary artery bypass graft, PCI: Percutaneous coronary intervention

Sacubitril/Valsartan was started for all patients. Clinical, laboratory and echocardiographic assessment were done at baseline and after 6 months. (Table 3) showed the clinical data at baseline and after 6 months. There was marked improvement of NYHA class, regression of cardiomegaly, neck veins congestion and lower limb edema with p value (0.000). Third heart sound and lung crackles disappeared with p value 0.017 and 0.003 respectively.

Table 3: Clinical data at baseline and after 6 months

		Frequency	Percent	P value
NYHA class at baseline	2	11	22	0.000*
	3	15	30	
	4	24	48	
NYHA class at 6 months	1	20	40	
	2	20	40	
	3	8	16	
	4	2	4	
Raised JVP at baseline	No	46	92	0.00
	Yes	4	8	
Raised JVP at 6 months	No	49	98	
	Yes	1	2	
S3 at baseline	No	32	64	0.017*
	Yes	18	36	
S3 at 6 months	No	47	94	
	Yes	3	6	
Crackles at baseline	No	28	56	0.003*
	Yes	22	44	
Crackles at 6 months	No	44	88	
	Yes	6	12	
LL edema at baseline	No	43	86	0.000*
	Yes	7	14	
LL edema at 6 months	No	46	92	
	Yes	4	8	
Shifted apex at baseline	No	33	66	0.000*
	Yes	17	34	
Shifted apex at 6 months	No	38	76	
	Yes	12	24	

Data are presented as frequency (%), *significant p value<0.05, NYHA: new york heart association, JVP: jugular venous pulse, S3: third heart sound, LL: lower limb

The results of the echocardiographic examinations were shown in (Table 4). There was marked improvement in the EDV, ESV and EF. At baseline they were found to be 193.996±69.5142, 142.538±63.7695 and 27.098±7.1668 respectively. After 6 months they were found to be 170.546±79.4744, 107.010±70.1144 and 40.546±12.8909, with p value of 0.002, 0.023 and 0.000 respectively.

Table 4: Echocardiographic data baseline and after 6 months

	N	Range	Minimum	Maximum	Mean	Std. Deviation	P value
0 EDV (ml^2)	50	349.0	87.0	436.0	193.996	69.5142	0.002*
6m EDV (ml^2)	50	405.3	71.7	477.0	170.546	79.4744	
0 ESV (ml^2)	50	315.0	55.0	370.0	142.538	63.7695	0.023*
6m ESV (ml^2)	50	369.2	29.8	399.0	107.010	70.1144	
0 IVSD (cm)	50	68.60	.40	2.08	.8300	.2631	0.987
6m IVSD (cm)	50	1.07	.33	1.40	.8574	.23108	
0 PWD (cm)	50	1.00	.50	1.50	.9034	.20700	0.548
6m PWD (cm)	50	.90	.40	1.30	.8958	.18499	
0 ESD (cm)	50	4.62	3.63	8.25	5.2848	.96920	0.021*
6m ESD (cm)	50	6.20	2.30	8.50	4.6336	1.23518	
0 EDD (cm)	50	4.47	4.40	8.87	6.12	0.93549	0.381
6m EDD (cm)	50	5.26	4.00	9.26	5.8194	1.13271	
0 LVM	50	424.40	63.20	487.60	219.5148	84.33501	0.243
6m LVM	50	320.70	105.70	426.40	202.8452	75.61464	
0 LVMI	50	196.1	36.1	232	114.2	36.32	0.254
6 LVMI	50	127.1	57.3	184.4	105.83	33.27	
0 EF%	50	24.0	11.0	35.0	27.098	7.1668	0.000*
6m EF%	50	57.0	15.0	72.0	40.546	12.8909	

Data are presented as mean ± SD or frequency (%), *significant p value<0.05, EDV: end diastolic volume, ESV: end systolic volume, IVSD: interventricular septum diameter, PWD: posterior wall diameter, ESD: end systolic dimension, EDD: end diastolic dimension, LVM: left ventricular mass, LVMI: left ventricular mass index, EF: ejaction fraction

Laboratory data showed marked reduction of serum level of Pro BNP from 1524±1922.704 to 594.898±1201.79 pg/ml with P value 0.001. The parameters of kidney function; namely serum creatinine, blood urea nitrogen (BUN) and estimated glomelular filtration rate (eGFR) showed mild changes. These changes, although they were statistically significant, they did not necessitate discontinuation of the medicine. Serum creatinine was mildly elevated from 0.93±0.245 mg/dl to 0.97±0.233 mg/dl with P value of 0.010. eGFR was mildly reduced from 85.044±24.84 to 79.76±22, with P value of 0.043. BUN was elevated from 28.6±11.8 to 32.32±11.54 mg/dl with P value of 0.001. Serum potassium level did not change significantly. At base line, it was found to be 4.25±0.427 mmol/L. After 6 months, it was found to be 4.33±0.48 with P value of 0.097. (Table 5).

Table 5: Laboratory data of the patients

	N	Range	Minimum	Maximum	Mean	Std. Deviation	P value
0m Hb%	50	8.4	10.0	18.4	13.766	1.5918	0.056
6m Hb%	50	7.8	9.4	17.2	13.320	1.5910	
0 Create	50	1.31	.49	1.80	.9302	.24507	0.010*
6m Create	50	1.09	.61	1.70	.9716	.23330	
0 BUN	50	49.5	12.5	62.0	28.610	11.8025	0.001*
6m BUN	50	50	18	68	32.32	11.545	
0 eGFR	50	113.4	33.0	146.4	85.044	24.8360	0.043
6m eGFR	50	93.6	35.5	129.1	79.762	22.0157	
0 Na	50	10	132	142	137.36	2.663	0.085
6m Na	50	18	128	146	138.44	3.786	
0m K	50	1.8	3.4	5.2	4.250	.4273	0.097
6m K	50	1.9	3.4	5.3	4.334	.4851	
ALT	50	140	10	150	37.58	28.839	--
Total cholesterol	50	174	112	286	167.58	43.325	__
TG	50	265	43	308	114.84	57.435	--
LDL	50	135	28	163	93.30	31.788	--
0m HbA1C	50	7.4	4.6	12.0	7.000	2.1797	
6m HbA1C	50	6.4	4.3	10.7	6.684	1.8449	0.023*
0 Pro BNP	50	8231	79	8310	1524.78	1922.704	
6m Pro BNP	50	6758.1	15.9	6774.0	594.898	1201.7862	0.001*

Data are presented as mean ± SD or frequency (%), *significant p value<0.05, Hb: hemoglobin, BUN: blood urea nitrogen, eGFR: estimated glomerular filtration rate, Na: sodium, K: potassium, ALT: alanine transaminase, TG: triglyceride, LDL: low-density lipoprotein, Pro BNP: natriuretic peptide tests measure levels of BNP.

Correlation between pro BNP at 6 months (6m) with differrent parameters showed that only 6m NYHA class, 6m EF, 6m EDV, 6m ESV, 6m EDD, and 6m ESD showed significant correlation with 6m pro BNP level. (Table 6).

Table 6: Correlation between 6 months pro BNP level with clinical and echocardiographic parameters

	6 months Pro BNP	
	F	P value
6 m NYHA	4.793	.018*
6 m Sys BP	.885	.637
6 m Dias BP	.690	.788
6 m pulse	1.080	.503
6 m EDV	4.525	.022*
6 m ESV	6.308	.008*
6 m IVSD	2.369	.117
6 m PWD	1.708	.236
6 m ESD	3.546	.042*
6 m EDD	3.462	.045*
6 m LVM	1.203	.432
6 m LVMI	1.277	.395
6 m EF%	6.762	0.030
6 m LAD	1.331	.369
6 m AO	.548	.892

* Significant p value<0.05, NYHA: New York heart association, SBP: systolic blood pressure, DBP: diastolic blood pressure, EDV: end diastolic volume, ESV: end systolic volume, IVSD: interventricular septum diameter, PWD: Posterior wall diameter, ESD: end systolic dimension, EDD: end diastolic dimension, LVM: left ventricular mass, LVMI: left ventricular mass index, EF: left ventricular mass index, LAD: left atrial diameter

Linear regression analysis was done between 6 months pro BNP and the factors that showed significant correlations with it; 6 m NYHA class, 6 m EF, 6 m EDV, 6 m ESV, 6m EDD, and 6m ESD. Only 6 months EDV, EF and NYHA class are still significantly correlated with the 6 months pro BNP, so that they can be used as indirect markers for LV remodeling. (Table 7).

Table 7: Linear regression analysis between 6 months pro BNP and 6m ESD, EDD, ESV, EDV, EF and NHYA class

Model	Unstandardized Coefficients		Standardized Coefficients	T	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
Constant	-3677.380-	1106.096		-3.325-	.002	-5906.571-	-1448.189-
6 m ESD	390.386	381.504	.401	1.023	.312	-378.485-	1159.258
6 m EDV	-13.784-	6.487	-.912-	-2.125-	.039	-26.858-	-.710-
6 m ESV	-1.108-	7.646	-.065-	-.145-	.885	-16.518-	14.302
6 m EDD	577.593	385.274	.544	1.499	.141	-198.876-	1354.062
6 m NYHA	854.089	169.032	.598	5.053	.000	513.428	1194.751
6 m EF	-28.623	12.806	-.307	-2.235	0.030	-54.732	-2.784.

NYHA: New York heart association, EDV: end diastolic volume, ESV: end systolic volume, IVSD: interventricular septum diameter, PWD: posterior wall diameter, ESD: end systolic dimension, EDD: end diastolic dimension

Regression analysis done between 6 months pro BNP and 6 months NYHA class showed persistent positive correlation. Regression analysis done between 6 months pro BNP and 6 months EDV also showed persistent positive correlation. Regression analysis done between 6 months pro BNP and 6 months EF showed persistant negative correlation. Figure 1.

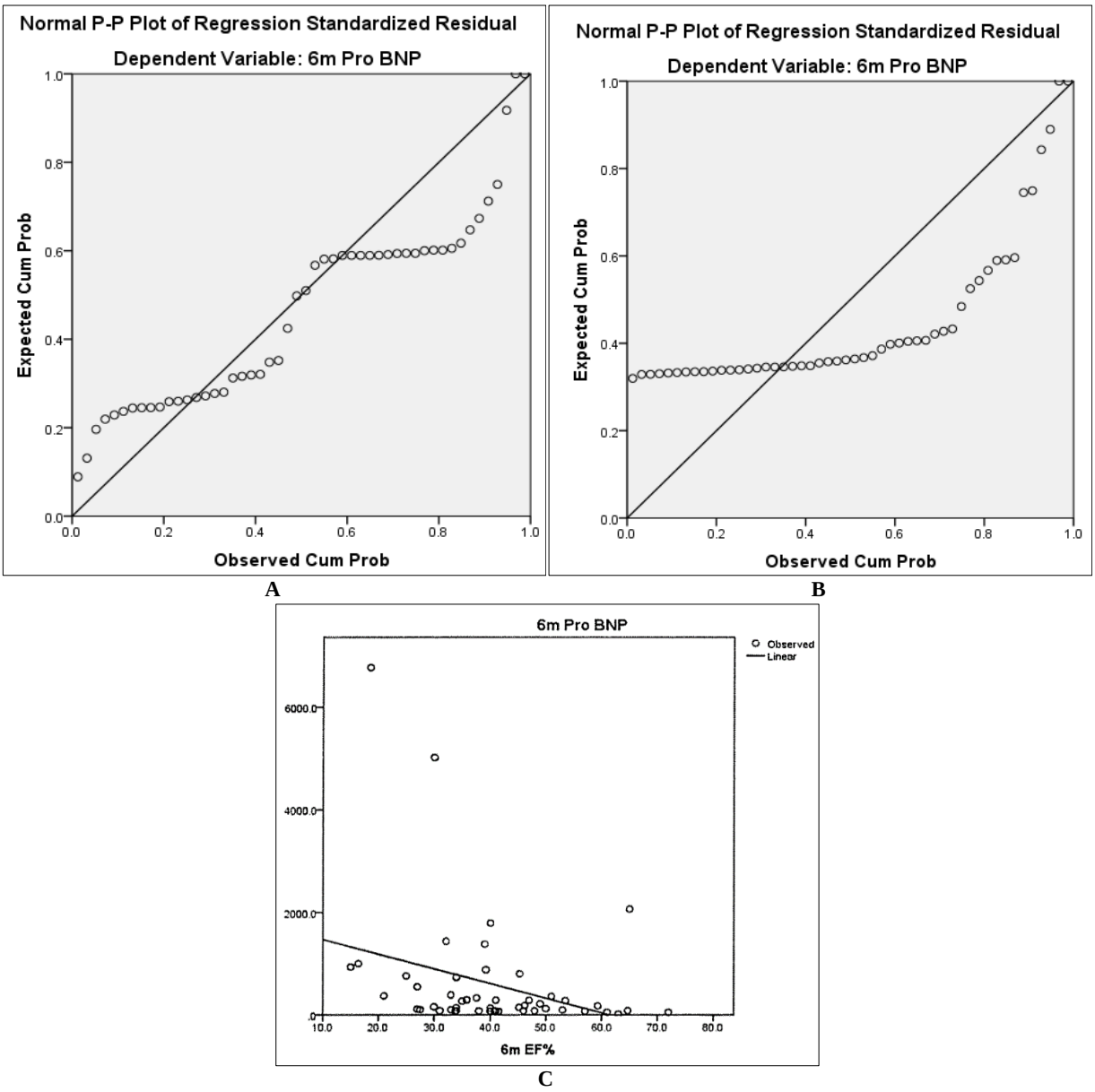

Fig 1: Regression analysis between 6 months pro BNP and A) NYHA class, B) EDV and C) 6 months TN-pro BNP and EF

Discussion

The most striking result of this work is that the addition of Sacubitril/Valsartan to the GDMT of HFrEF patients was associted with marked reduction in serum level of Pro BNP, which reflected reverse remodeling of the LV, as indicated by improvement in the echocardiographic parameters of remodeling, namely EDV, ESV and EF [4]. The mean systolic blood pressure (SBP) and SD at the start of the study were 126.60±15.886 mmHg. After 6 months; the mean SBP and SD were 126.28±15.063 mmHg. P value of (0.235).

Mean diastolic blood pressure (DBP) and SD at baseline were found to be 72.04±9.877 mmHg. After 6 months, the mean DBP and SD were found to be 68.42±8.999 mmHg with a P value of (0.530). This means that the effect of Sacubitril/Valsartan on both systolic and diastolic BP is not remarkable. This was in contrast to the study of De Vecchis R *et al*. [5] who did a meta-analysis of the studies used Sacubitril/Valsartan to treat hypertension in 1513 elderly patients. They found that Sacubitril/Valsartan reduce BP effectively in such groups of patients. The difference between their results and the present study may be explained by the fact that they used the drug in elderly hypertensive people only, and the improvement of the EF in this study may compensate for the reduction in the BP.

The mean HR and SD at baseline were found to be 86.82±11.999 beat/minute. After 6 months, the mean HR and SD at baseline were found to be 74.48±10.34 beat/minute. P value of (0.017). This means that Sacubitril/Valsartan reduces the tachycardia associated with HFrEF significantly. This result was in agreement with the results of Bunsawat K, *et al*. [6]. The individual that conducted research on the sympathoinhibitory impact of Sacubitril/Valsartan in patients with HFrEF. The researchers determined that this medication reduced the baseline sympathetic activity in individuals with HFrEF after a short period of therapy. 7 Sacubitril/Valsartan administration resulted in a substantial enhancement in the NYHA classification in the patients. This was in agreement with the study of Zhang R *et al*. [7] who showed that Sacubitril/Valsartan therapy obviously improved NYHA class from 2.3 +0.6 to 1.8 + 0.5 ($p< 0.001$).

The use of Sacubitril/Valsartan significantly improved the echo parameters of remodeling, namely the EDV, ESV and LVEF, with P values of 0.002, 0.023 and 0.000 respectively. The improvement of the echo parameters with the use of Sacubitril/Valsartan in patients with HFrEF was in agreement with the results of the study done by Landolfo M *et al*. [8] who conducted research on the impact of Sacubitril/Valsartan on clinical and echocardiographic factors in outpatients suffering from heart failure and decreased ejection fraction. The researchers determined that there was a significant improvement in left ventricular ejection fraction (LVEF), left ventricular diameters and volumes, pulmonary artery pressure (PAP), and left atrial diameter, as compared to the initial measurements.

The serum creatinine and BUN levels were found to be mildly elevated with P value of 0.010 and 0.001. eGFR level was mildly reduced with a P value of 0.043.

According to these results, Sacubitril/Valsartan use was associated with a little increase in the renal functions, but this change did not reach a level that needs reduction in the dose or withdrawal of the drug.

This was in agreement with the results of the study done by Spannella F *et al*. [9] who made a systemic review for the effects of this drug on kidney functions and concluded that Sacubitril/Valsartan exerted reno-protective effect on the kidneyRegarding the reduced likelihood of exacerbating renal function decline. Patients administered with Sacubitril/Valsartan had a 30% reduced likelihood of experiencing renal events and a reduction in eGFR.10

Paolini C *et al*. [10] Additionally, it was determined that there was a significant rise in creatinine serum levels, from an average of 1.17±0.31 mg/dL to 1.27±0.40 mg/dL (p = 0.01). Furthermore, the estimated glomerular filtration rate (eGFR) fell from an average of 61.0±22.1 mL/min/1.73 m2 to 57.5 ± 19.6 mL/min/1.73 m2 (p = 0.02)

The administration of Sacubitril/Valsartan did not result in substantial alterations in the serum potassium level, as shown by a P value of 0.097. This finding aligns with the findings of the research conducted by Ferreira JP *et al*. [11] which examined the levels of serum potassium in the PARADIGM HF trial. Their conclusion was that Sacubitril/Valsartan had no significant impact on potassium concentrations when compared to Enalapril.

There was marked reduction of the level of Pro BNP from 1524.78±1922.704 to 594.898±1201.7862 pg/dl, with P value 0.001. This reduction in the level of pro BNP could be attributed to the reduction in the left atrial dimension and the left ventricular volumes. These findings align with the results of a research conducted by Liu LW *et al*. [12] which concluded that Sacubitril/Valsartan had a notable impact on enhancing LVEF, left ventricular reverse remodeling, and reducing NT-pro BNP levels in the Taiwanese population.13

The results of the present study showed that only 6m NYHA class, 6 m EF, 6 m EDV, 6 m ESV, 6m EDD, and 6m ESD showed significant correlation with 6m pro BNP level. These results are contradictory to the results of the study done by Murphy SP *et al*. [13] who studied Atrial Natriuretic Peptide and Treatment with Sacubitril/Valsartan in HFrEF. The researchers discovered a considerable correlation ($r = 0.699$; $p< 0.001$) between the initial values of ANP and LAVI. However, after starting Sacubitril/Valsartan treatment, the changes in ANP were even more closely linked to decreases in LAVI than to changes in LVEF.

Linear regression analysis was done between 6 months Pro BNP and the factors that showed significant correlation with it; 6m NYHA class, 6m EF 6m EDV, 6m ESV, 6m EDD, and 6m ESD. Only 6 months EDV, EF and NYHA class are still significantly correlated with the 6 months pro BNP level so that they can be used as indirect markers for LV remodeling. To the best of our knowledge, this may be the first study to find a strong correlation between simple echocardiographic parameter (EDV and EF) and clinical parameter (NYHA class) and the reduction of pro BNP.

Limitation: This study was conducted on small sample of only 50 patients. Another study with a larger number of patients would be of a great help to confirm the results. Also, this study was carried out in a single center. Examining more patients in different centers will enhance the accuracy of the results. The addition of other echo parameters, e.g., left ventricular global strain could be of help to fine-tune our results.

Conclusion

From the results of the present study, the conclusion was: there was marked reduction in the level of TN-pro BNP after the use of Sacubitril/Valsartan in patients with HFrEF. This reduction in the level of TN-pro BNP was associated with improvement in clinical and echocardiographic Parameters. 6 months EDV, EF and NYHA class are still significantly correlated with the 6 months TN-pro BNP so that they can be used as indirect markers for LV remodelling.

Acknowledgements

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Disclosure statement
No potential conflict of interest was reported by the authors.

Funding
Non-funding.

Financial support and sponsorship: Nil

Conflict of Interest: Nil

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How to Cite This Article
Abdelhalim MI, Elsharnouby KA, Amrousy MZE, Elsokkary HM. Role of brain natriuretic peptide as an indicator for reverse remodeling of left ventricular systolic dysfunction after introduction of sacubitril / valsartan in patients with heart failure with reduced ejection fraction. International Journal of Cardiology Sciences. 2024;6(1):21-27.